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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 11/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,160	ROSEY ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-21,25-29 and 34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,30-33 and 38-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment filed on 8/29/2003, paper # 12 is acknowledged. Claims 1-50 are pending in the application.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), certified copy of Australia 1381/00 filed on11/20/2000 has been placed of record in the file. Applicant's also claim domestic priority to provisional application 60/249,595 filed on 11/17/2000 is also acknowledged. Accordingly priority is accorded as of 11/17/2000 for the elected claims.

Drawings

3. The drawings are objected to by the draftsperson under 37 C.F.R. 1.84 or 1.152. See PTO-948 for details.

Information Disclosure Statement

4. Information Disclosure Statement filed on 5/7/02 (Paper # 5) is acknowledged and a signed copy is attached to this Office action.

Specification - Informalities

5. Applicant should follow the direction or order or arrangement in framing the specification as provided in 37 CFR 1.77(b) since this is a utility application filed in USA. The specification should include all the sections in order. For example: Claims should begin with "I claim" or "'we claim" or "What is claimed is" Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Election/Restriction

6. Applicant's election of Group II, Claims 22-24, 30-33and 37-50 with traverse with respect to SEQ.ID.NO: 1 corresponding to plasmid pGTE # 2 Accession Number: NM00/16477 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that all of the groups of claims relate to the gene and polypeptides encoded by the gene and claims are generally relate to novel therapeutic compositions for the treatment of disease caused by L. intracellularis. Further, the applicant requests the examiner to prosecute all the groups, as it is well accepted practice in the Office to prosecute all the groups in a single application because search and examination would not be an undue burden. This is not found persuasive.

The specification recites that various nucleotide sequences SEQ.ID.NO: 1, 3, 5, 7, 9, 11, 13, 15 and 17 encoding various polypeptides. Each polypeptide is presented in sequence identifiers as SEQ.ID.NO: 2, 4, 6, 8, 10, 12, 14, 16 and 18 respectively. Each nucleotide sequence has bee cloned and deposited as a separate plasmid and each obtained a specific accession number. Accession NO (NMOO/1647630 (plasmid pGTE # 1 g1nH); NMOO/16477 (plasmid pGTE # 2 flhB); NMOO/16478 (plasmid pGTE # 3 fliR); NMOO/1 6479 (plasmid pGTE # 4 motA/B); NMOO/1 6480 -86-(plasmid pGTE # 5 tlyC); NMOO/164811 (plasmid pGTE # 6 ntrC); NMOO/116482(plasmid pGTE # 7 ytfM); and NM01/23286 (plasmid pGTE # 8 ytfN) .

These nucleotide sequences appear to be novel in encoding unique polypeptide. For example SEQ.ID.NO: 1 comprises 622 nucleotides encoding a protein that contains 207 amino acids (SEQ.ID.NO: 2) and SEQ.ID.NO: 5 comprises1371nucleotides encoding a protein that contains 456 amino acids (SEQ.ID.NO: 6). Therefore, these two nucleotide sequences encoding two unique proteins are considered as distinct inventions and are properly restricted under 35 U.S.C. 121.

literature searches for each of the sequences, both of which are particularly relevant in this art, are not co-extensive and are much more important in evaluating the burden of search. For example, search and examination issues for different proteins and vaccines are different. Clearly different searches and issues are involved in the examination of each group.

However, if a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

7. Claims 1-21, 25-29 and 34-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

8. Claims 22-24, 30-33 and 38-50 will only be examined to the extent they read on the elected invention of SEQ.ID.NO: 1 corresponding to plasmid pGTE # 2 Accession Number NM00/16477. All other SEQ.ID.NOS are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, said election made in Paper # 12.

Applicant is advised to amend claims to the elected invention SEQ.ID.NO: 1 corresponding to plasmid pGTE # 2 Accession Number NM00/16477.

Claim Rej ctions - 35 U.S. C. 112, first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 22-24, 30-33 and 38-50 with are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete information how to make the plasmid pGTE # 2 flhB (Accession number obtained at Netherlands, NMOO/16477). The specification teaches general description of amplifying the amino acid coding gene and making an expression vector. However, it fails to teach that the specific *Lawsonia cellularis* nucleic acid sequence SEQ.ID.NO: 1 that has been cloned as an expression plasmid pGTE # 2 flhB. In the absence of such a disclosure, the deposit of the NMOO/16477, plasmid pGTE#2 flhB is required. It is not clear that the expression plasmid pGTE#2 flhB are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Because one skilled in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the expression plasmid pGTE#2 flhBof the invention, a suitable deposit for patent purposes, evidence of public availability of the

expression plasmid pGTE # 2 flhB of the invention or evidence of the reproducibility without undue experimentation of the expression plasmid pGTE # 2 flhB is required.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposits have not been made under the provisions of the Budapest Treaty; then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;

2) The name and address of the depositor;

3) The date of deposit;

4) The identity of the deposit and the accession number given by the depository;

5) The date of the viability test;

6) The procedures used to obtain a sample if the test is not done by the depository; and

7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the plasmid pGTE # 2 flhB, described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the

biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR1.801-1.809 for further information concerning deposit practice.

The ATCC's address, effective March, 23,1998 is

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11. Claims 22-24, 30-33 and 39-50 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

The claims are drawn to Lawsonia intracellularis vaccine vector or isolated nucleic acid molecule comprising a nucleic acid having a protein encoding a nucleic acid sequence having at least about 60% sequence identity to nucleic acid sequence SEQ.ID.NO: 1, at least about 60% sequence identity to nucleic acid sequence NMOO/16477 (plasmid pGTE # 2 flhB), a protein encoding a nucleic acid sequence comprising at least about 15 contiguous nucleotides of a nucleic acid sequence SEQ.ID.NO: 1, a protein encoding a nucleic acid sequence comprising at least about 15 contiguous nucleotides of a nucleic acid sequence NMOO/16477 (plasmid pGTE # 2 flhB), a protein encoding a nucleic acid sequence which hybridizes at least under low stringency to the complement of a nucleotide sequence SEQ.ID.NO: 1, a protein encoding a

nucleic acid sequence which hybridizes at least under low stringency to the non coding strand of DNA contained within a plasmid NMOO/16477 (plasmid pGTE # 2 flhB), a homologue , analogue,derivative of said nucleic acids and an isolated nucleic acid encoding flhB

(The examiner is considering all these as variants).

The specification broadly describes as part of the invention, an isolated nucleotide sequence of SEQ ID NO: 1, which contains 622 nucleotides obtained by cloning *Lawsonia intracellularis* DNA. However, the specification does not teach variants of Lawsonia intracellularis encoding a nucleic acid molecules.

The actual biological function of a protein encoding nucleic acid SEQ ID NO: 1 and as a vaccine composition is not set forth in this specification. Applicants broadly describe the invention as embracing any deletion by use of language in which a specified percent of amino acids can be changed in the protein. USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

The specification only discloses a vaccine vector or a polynucleotide sequence consisting of SEQ ID NO: 1 which corresponds to the polynucleic acid sequence encoding the Lawsonia intracellularis protein comprising the amino acid sequence, SEQ ID N0: 2. An isolated polynucleotide comprising a nucleotide sequence encoding SEQ ID NO: 2, is also described by way of the written description in view of the art established principle of wobble variants of triplet codons for particular bacterial amino acids as described in basic textbooks. Thus, an isolated polynucleotide sequence comprising the SEQ ID NO: 1 and an isolated polynucleotide

comprising a nucleotide sequence encoding the amino acid sequence SEQ ID NO: 2 meet the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below. The specification fails to teach the claimed variants and they do not exist as an invention independent of their function in encoding a protein. The actual structure or other relevant identifying characteristics of each variant including homolog, analogue or derivative having the claimed properties can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. variants,) and testing each to determine whether such a variant has any particularly disclosed properties of a protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function. This specification does not teach such, and the art is devoid of this correlation for SEQ ID NO: 1, with undetermined function. There is no written description support for variants as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

12. Claims 22-24, 30-33 and 39-50 also rejected under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated Lawsonia intracellular vaccine vector comprising the plasmid pGTE # 2 flhB or an isolated polynucleotide comprising the nucleotide sequence SEQ ID NO: 1 or an isolated polynucleotide comprising the nucleotide sequence SEQ ID NO: 1 encoding the polypeptide flhB, SEQ.ID.NO: 2, the specification does not reasonably provide enablement Lawsonia intracellularis vaccine vector or isolated nucleic

acid molecule comprising a nucleic acid having a protein flhB encoding a nucleic acid sequence having at least about 60% sequence identity to nucleic acid sequence SEQ.ID.NO: 1, at least about 60% sequence identity to nucleic acid sequence NMOO/16477 (plasmid pGTE # 2 flhB), a protein encoding a nucleic acid sequence comprising at least about 15 contiguous nucleotides of a nucleic acid sequence SEQ.ID.NO: 1, a protein encoding a nucleic acid sequence comprising at least about 15 contiguous nucleotides of a nucleic acid sequence NMOO/16477 (plasmid pGTE # 2 flhB), a protein encoding a nucleic acid sequence which hybridizes at least under low stringency to the complement of a nucleotide sequence SEQ.ID.NO: 1,), a protein encoding a nucleic acid sequence which hybridizes at least under low stringency to the non coding strand of DNA contained within a plasmid NMOO/16477 (plasmid pGTE # 2 flhB), a homologue , analogue and derivative of said nucleic acids (the examiner is considering all these as variants). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims since there is no written description support for the claimed invention.

The specification is not enabled for any variants of a polynucleotide comprising SEQ ID NO: 1 because 1) the specification fails to teach that the alleged protein of SEQ ID NO: 2 is able to function as a diagnostic by binding immune sera from convalescent patients; 2) the specification fails to teach how to make and use nucleic acid sequences which encode variants thereof that have an unknown and uncharacterized function; 3) the specification fails to teach what are the critical nucleic acid and protein residues that can be modified and still achieve a nucleic acid encoding a protein with similar functional activity or any variant nucleic acid diagnostic characteristics or any nucleic acid with immunogenic/pharmaceutical/vaccine characteristics *for Lawsonia intracellularis* 4) the art teaches that proteins with replacement of

single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of the protein of SEQ ID NO:2 or diagnostic or vaccine use of variants thereof, and the claimed vaccine use of the isolated nucleic acids comprising SEQ ID NO:1 and variants thereof, isolated nucleic acids encoding the protein and variants thereof and 5) applicants have not displayed a nexus between the structure of the gene sequence and function of the protein as a vaccine or as a diagnostic protein. As to points 1)- 5), the specification fails to provide a written description of any protein variants (i.e. homologs, hybridizing homologs, hybridizing sequences of the bacterial protein sequence of SEQ ID N0: 2 and the corresponding encoding polynucleic acids, which function equivalently to a polypeptide comprising the disclosed SEQ ID NO: 2 or are able to be used as a vaccine or diagnostic. The specification fails to teach the critical protein residues involved in the function of the protein SEQ ID NO: 2, such that the skilled artisan is provided no guidance to test, screen or make nucleic acid sequence variants of the polynucleic acids encoding the variants of the polypeptide of comprising SEQ ID NO: 2 or the polynucleotide comprising SEQ ID NO: 1, using conventional technology which allow for a screening or generic vaccine or diagnostic use in the specification. The specification fails to teach to what extent you could alter SEQ ID NO: 1 and still present the sequence as diagnostic or a vaccine. In order to be diagnostic the sequence must distinguish *for Lawsonia intracellularis* from other clinically relevant autochthonous bacteria in a host. The specification also fails to demonstrate the actual biological function of the DNA and protein and only assigns it a putative characteristic as a protein. Even if one were to use the in vivo vaccine methodology of the specification to screen for vaccine variants, one of skill in the art would be reduced to merely randomly altering nucleic acids and amino acid(s) which would lead to

unpredictable results regarding the functional activity of the DNA encoding protein and the ability of the nucleic acid to be used as a vaccine.

Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol, 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition.

Applicants have not taught which residues of SEQ ID NO: 2 can be varied and still achieve a protein that is functional as a vaccine or is capable of use as a diagnostic using immunological means of recognition. The specification has not conceived any other functionally equivalent protein variant or the polynucleic acid sequence encoding the protein variant or homolog and does not set forth the general tolerance to substitutions and where substitutions could be made. Since, the specification lacks a written description of any variant or homolog of SEQ ID NO: 1 or any protein sequence comprising SEQ ID NO: 2, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed polynucleotide encoding protein variants of SEQ ID NO: 2 respectively, as well as how to use the polynucleotides encoding the protein variants, one of skill in the art would be unable to produce these polynucleotides encoding protein variants or polynucleotide variants encompassed by the instant claims. Further, if one nucleotide is deleted or inserted at a single place within the coding sequence, all the codons down stream of that insertion or deletion will be frame shifted. If that frame shift takes place near the 5' end of the gene, it is highly likely that the protein expressed will have little in common structurally or functionally with the protein. Applicants simply cannot predict what effect a given change in the nucleic acid sequence will cause. Such changes are not enabled as applicants' invention, which is disclosed as a protein. In this regard, applicant has not enabled the scope of the invention as claimed for those nucleic acids, which would be altered as now claimed. The specification discloses a novel *Lawsonia intracellularis* protein and a nucleic acid encoding it. The protein has specific immunological and biological properties, which are the result of its primary acid sequence as encoded by this nucleic acid sequence. Applicants' proposed variations do not predict a protein having all the identifiable properties of a protein, SEQ.ID.NO: 2 as disclosed. Therefore, such undisclosed and unidentified nucleic acids which result from these, insertions, deletions or substitutions

encompasses by the recited "at least 60% identical" to an polypeptide encoded by an undefined reading frame from SEQ ID NO-.1 are not enabled for their scope. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed scope of invention. Although the skilled artisan might envision making a great number of changes of a reference nucleic acid sequence in accordance with applicant's disclosure, it is unclear exactly that the protein which is expressed therefrom would be a protein SEQ.ID.NO: 2 as applicants' invention. These altered nucleic acids would encode a polypeptide, which would vary from the disclosed amino acid sequence in some unknown or unpredictable manner. Amgen Inc. v. Chugai Pharmaceutical Co. Inc. 18 USPQ2d 1016, 1026 (CAFC 1991) addressed a similar issue of enablement and undue experimentation for analogs of erythropoietin (EPO) gene broadly claimed and narrowly disclosed. In that instance, it was found that: over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substitution three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA sequences encoding sequences that can produce EPO-like product is potentially enormous. Further, at page 1027, the CAFC found that: it is not necessary that a patent applicant test all the embodiments of his invention,.... what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, this means disclosing how to make and use enough sequence to justify a grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all of the Wands factors to find a disclosure enabling. They are not illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences to support its all-encompassing claims... Here, however, despite extensive statements in the

specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analogs genes are disclosed. Amgen argue that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO analogs. There may be other genetic sequence that code for EPO-Type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them ...[W] e do not intend to imply that genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure of hot to make EPO and a very few analogs.

Finally, at page 1028, the CAFC concludes: Considering the structurally complexity of the EPO gene, the manifold possibilities for change in its structure, with an attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient; having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that generic DNA sequence claims are invalid under section 112. See also In re Duel 34 USPQ2d 1210 (CAFC 1995); Colbert v. Lofdahl 21 USPQ2d 1068 (Bd. Pat. Ap. Inter. 1991); and University of California v. Eli Lily and Co. 43 USPQ2d 1398 (CAFC 1997). Additionally, with respect to claims 22-24, nucleic acids require expression control sequences in order to promote transcription and translation of the open reading frame, absent these sequences the open reading frame will not be translated into

protein and the protein not produced. As such, absent expression control sequences the method for producing a polypeptide will not work for the production of any nucleic acid encoding a polypeptide. In view of the lack of written description of any nucleic acid encoding a protein variant, the lack of enabling description of make and use polynucleotides encoding protein variants of SEQ ID NO: 2, the lack of an enabling written description of how to obtain and make and use the nucleic acid variants of the of the amino acid of SEQ ID NO:I or 2, the unpredictability associated with making and using the nucleic acids encoding the myriad variants of SEQ ID NO 1 or: 2 encompassed in the scope of the claims as set forth above, the lack of teaching even a beginning point for variation of the nucleic acid corresponding to a variant-of-the protein sequence of SEQ ID NO: 2 for routine experimentation, lack of working examples commensurate in scope with the instant claims, the skilled artisan would be forced into undue experimentation to practice (i.e. make and use) the invention as is broadly claimed.

Claims 22-24 are drawn to a vaccine vector compositions. The specification provides no information on the immunogenicity of protein encoded by the nucleic acid, the claimed fragments, the variants or the ability of such to protect from disease. The specification fails to teach that the claimed nucleic acids encoding the polypeptide or fragments are capable of generating a humoral or cellular immune response. The specification also fails to teach that the immune/antibody response to the polypeptide produced by the nucleic acid, alone or in combination with adjuvants or carriers provides for a protection against infection in any acceptable animal model. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient to provide for enablement of vaccines. This specification fails to teach any immune response generated by means of a nucleic acid --vaccine. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of

"VACCINES" [Plotkin, 5.A. et al. (eds) published by W. B. 5aunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one of the claimed polynucleotide encoding polypeptides or fragments thereof alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. The specification fails to teach that the claimed polynucleotide encoding a polypeptide peptide or fragment or variant thereof are able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize other similar nucleic acids as operative vaccines. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/5 Ltd., 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made-and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (In re Wright, 27 U5PQ2d 1510).

The state of the prior art indicates little is known about the humoral and, especially, cell-mediated immune response in pigs exposed to Lawsonia intracellularis. Pathogenesis of L. intracellularis has not been well investigated; however, organisms cultured in vitro have been used successfully to reproduce the disease in vivo. This bacterium has a tropism for intestinal epithelial cells, and the major pathological consequence of infection is hyperplasia of infected epithelial cells. The specific bacterial determinants which confer pathogenicity and cause these distinctive pathological effects are not known (see McCluskey et al, Infect Immun 2002 Jun; 70(6): 2899-907) Bacterial attachment and entry occur via the apical surface of immature

epithelial cells in a process which appears to require a specific bacterial ligand-receptor interaction and once inside the cell, the bacteria escape from the vacuolar compartment into the cytoplasm, where they multiply and spread from cell to cell following cell division. At present, the determinants used by L. intracellularis to enter the cell, escape the vacuole, multiply intracytoplasmically, and modulate host cell function are not known. Therefore, the claimed outer-membrane protein induces an effective immune response such that it can be used, as a vaccine composition is not predictable in this underdeveloped art. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for any *in vivo* uses of the claimed protein.

In the absence of a teaching of the claimed nucleic acids encoding polypeptides can generate an immune response and that immune response is effective in prevention of disease, the specification is not be enabled for vaccines. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

Claim Rejections - 35 USC 112, second paragraph

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 22-24, 31-33, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 33 are rejected as being vague for the recitation of "a protein encoding nucleic acid sequence." Generally protein is encoded by a nucleic acid or a nucleic acid encodes a protein.

Claims 22 and 31 are rejected as being vague for the recitation of "low stringency". It is not clear what are these low stringency conditions?

Claims 22, 31 are rejected as being vague for the recitation of "homologue", "analogue" and derivative". It is not clear what are the metes and bounds of these terms?

Status of Claims

15. No claims are allowed.

16. Accession NO, NMOO/16477 (plasmid pGTE # 2 flhB) and an isolated nucleic acid which consists of a nucleotide sequence, SEQ.ID.NO: 1 encoding the polypeptide SEQ.ID.NO: 2 are free of prior art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D

11/11/03

MARK NAVARRO
PRIMARY EXAMINER